CLINICAL STUDY PROTOCOL

A Multicenter, Double-Blind, Parallel-Arm, Placebo-Controlled, Phase 2 Study of the Efficacy, Safety, and Tolerability of Oral Full-Spectrum Microbiota® (CP101) in Subjects with Recurrence of *Clostridium difficile* Infection (PRISM3)

Sponsor:	Finch Research and Development LLC 200 Inner Belt Road, Suite 400 Somerville, MA 02143
Protocol Number:	CDI-001
IND Number:	17336
Investigational Product:	Full-Spectrum Microbiota® (CP101)
Indication:	Recurrent *Clostridium difficile* infection (CDI)
Development Phase:	2
Sponsor's Responsible Medical Officer:	[redacted]
Version:	Version 3.0 (22 December 2016) Version 4.0 (13 March 2017) Amendment 01 Version 5.0 (31 August 2017) Amendment 02 Version 6.0 (22 February 2018) Amendment 03 Version 7.0 (01 March 2019) Amendment 04

SPONSOR SIGNATURE PAGE

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Protocol (Version) Date:	01 March 2019

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number:	CDI-001
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Protocol (Version) Date:	01 March 2019

I acknowledge that I have read and understand the protocol named above and agree to conduct the study according to the protocol named above. I also agree and will adhere to terms and procedures in accordance with United States Food and Drug Administration (FDA)/International Council for Harmonisation (ICH) guidelines, including all federal and locally applicable regulations and laws.

I assure that the study drug supplied by the Sponsor will be used only as described in the protocol named above.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

1.0 DOCUMENT HISTORY

The summary of changes was moved to a separate document.

2.0 SYNOPSIS

Title of Study:

A Multicenter, Double-Blind, Parallel-Arm, Placebo-Controlled, Phase 2 Study of the Efficacy, Safety, and Tolerability of Oral Full-Spectrum Microbiota® (CP101) in Subjects with Recurrence of *Clostridium difficile* Infection (PRISM3)

Protocol Number: CDI-001	**Phase of Development:** 2
Test Drug: Oral Full-Spectrum Microbiota® (CP101)	**Indication:** Recurrent *Clostridium difficile* infection (CDI)

Study Centers: Approximately 65 study sites in the United States and Canada

Objectives:

The objectives of this Phase 2 study are:

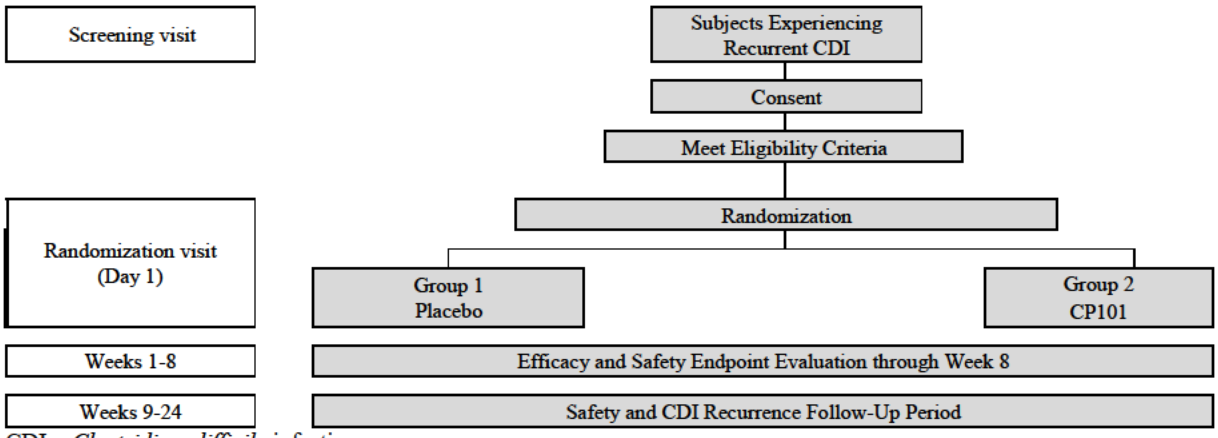
- To evaluate the safety and tolerability of CP101 treatment compared to placebo in adults with previously treated recurrent CDI.
- To evaluate the efficacy of CP101 treatment relative to placebo in adults with previously treated recurrent CDI

Methodology:

This is a double-blind, placebo-controlled, parallel-arm, multicenter study comparing the safety, tolerability, and efficacy of CP101 treatment relative to placebo in adults with previously treated recurrent CDI. Subjects who are experiencing recurrent CDI will undergo screening procedures. Subjects who meet eligibility criteria will be randomized to study drug.

[redacted] including active drug (CP101) and placebo. Subjects will be monitored for recurrence of CDI, safety, and tolerability for 24 weeks following Randomization. The primary efficacy and safety endpoints will be evaluated at 8 weeks post-treatment, and all subjects will continue to be followed for an additional 16 weeks for safety and recurrence of CDI.

To qualify for the study, subjects must be experiencing recurrent CDI defined as: a) ≥ 3 episodes of CDI, with 2 episodes occurring within the previous 12 months (inclusive of the current episode); OR b) 2 episodes of CDI occurring within the previous 6 months (inclusive of the current episode) AND 65 years of age or older. Additionally, to qualify, recurrent CDI subjects must have received standard-of-care CDI antibiotics for the most recent CDI episode (for 10-42 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator) and have an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during standard-of-care CDI antibiotics prior to Randomization.



CDI = *Clostridium difficile* infection.

The primary clinical outcome is recurrence of CDI and is defined as a) diarrhea (> 3 unformed stools [Bristol Stool Scale score of 6 or 7] per day) for 2 or more consecutive days; b) a stool specimen testing positive for *Clostridium difficile* (*C. difficile*) by a testing algorithm (see figure below); and c) requiring a course of standard-of-care CDI antibiotics. Secondary outcomes include assessment of decolonization of antibiotic-resistant bacteria (ARB) and [redacted]

Subject Population:

Approximately 200 subjects 18 years of age or older, who experience recurrent CDI, and who respond to a standard-of-care CDI antibiotic regimen for the most recent CDI episode will be randomized to study drug.

Inclusion/Exclusion Criteria:

Study eligibility will be evaluated during the Screening visit, which will take place prior to the Randomization visit (Day 1).

Inclusion Criteria:

1. Ability to provide written informed consent;
2. Men or women 18 years of age or older;
3. Recurrent CDI* as defined by:
   a) ≥ 3 episodes of CDI, with 2 episodes occurring within the previous 12 months (inclusive of the current episode); OR
   b) 2 episodes of CDI occurring within the previous 6 months (inclusive of the current episode) AND 65 years of age or older;

   *NOTE: CDI is defined by:
   a) History of diarrhea (≥ 3 unformed stools per day) for 2 or more consecutive days; AND
   b) A stool specimen documented as testing positive for *C. difficile* within 60 days prior to Randomization. Testing for CDI may include:
      - [redacted]
      - [redacted]

[redacted]

AND

c) Has received a course of standard-of-care CDI antibiotics for the most recent CDI episode (for 10-42 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator); AND

d) Has an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during standard-of-care CDI antibiotics prior to Randomization.

4. Willingness to abstain from consuming non-dietary probiotics through Week 8 after Randomization;
5. Women must fulfill at least 1 of the following criteria:
   a) Post-menopausal, defined as amenorrhea ≥ 1 year;
   b) Surgically sterile: hysterectomy, bilateral oophorectomy, or tubal ligation; or
   c) Abstinent or willing to use adequate contraception from Screening through the Week 24 visit, per Section 11.2; and
6. Deemed to have life expectancy of 8 weeks or greater.

Exclusion Criteria:

1. Admitted to, or expected to be admitted to, an intensive care unit for any medical reason;
   a) NOTE: Residents of long term care facilities, such as nursing homes and rehabilitation centers, are eligible for study entry;
   b) NOTE: Patient visits to clinics, urgent care centers, acute care hospitals, or emergency departments are allowed; however, subject must be an outpatient prior to Randomization;
2. Stools known to be positive for ova and/or parasite(s), or other enteric pathogens (e.g., *Salmonella*, *Shigella*, and/or *Campylobacter*) within 28 days prior to Screening;
3. Inability to ingest capsules (e.g., severe nausea, vomiting, and/or dysphagia);
4. Known or suspected toxic megacolon and/or known small bowel ileus;
5. Prior history, evidence, or diagnosis of inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, indeterminate colitis, or microscopic colitis);
6. Recent diagnosis (< 6 months prior to Screening) of diarrhea-predominant irritable bowel syndrome (post-infection or not related to an enteric infection). Subjects with diarrhea-predominant irritable bowel syndrome ≥ 6 months prior to Screening may be randomized after consultation with the Medical Monitor;
7. Current diagnosis of chronic diarrheal illness with pre-CDI baseline diarrhea (≥ 3 loose stools in a 24-hour period). This includes but is not limited to celiac disease, bile salt diarrhea, chronic pancreatitis, and short gut syndrome;
8. Past administration of bezlotoxumab (Zinplava™), or past enrollment in a *C. difficile* vaccine study within 12 months of Randomization;
9. Initiation of any systemic cancer treatment (e.g. chemotherapy, radiotherapy, biologic, others) for active malignancy that is planned 8 weeks prior to Randomization or during the 8 weeks following Randomization. Subjects on maintenance treatment for malignancy may be randomized after consultation with the Medical Monitor;
10. Initiation or escalation of immunosuppressive agents, at the discretion of the Investigator, for any condition during the 8 weeks prior to Randomization or planned during the 8 weeks following Randomization. Subjects on stable immunosuppressive agents or short-courses may be randomized after consultation with the Medical Monitor. NOTE: Solid organ transplant recipients are excluded;
11. Compromised immune system, including, but not limited to, a known history of human immunodeficiency virus infection and cluster of differentiation 4 count that is unknown or

documented to be < 200 cells/mm^3 within the last year, or an acquired immunodeficiency syndrome-defining illness; or at the discretion of the Investigator;

12. Fecal transplant for any condition, regardless of route of administration, in the last year or plans to undergo during the study;
13. Major intra-abdominal surgery (e.g., bowel resection) within the past 60 days prior to Screening (excluding appendectomy or cholecystectomy), history of total colectomy/ileostomy and/or planned invasive surgery/hospitalization during the study;
    a) NOTE: Subjects with history of bariatric surgery may be randomized after consultation with the Medical Monitor;
14. Use of a systemic antibiotic for any condition (other than CDI therapy for the current recurrence) during the Screening period, or any anticipated use of a systemic antibiotic for any condition other than CDI during the study for 8 weeks after Randomization. This includes subjects who have a known medical procedure that requires antibiotic prophylaxis (e.g., elective surgical procedure or dental procedure requiring prophylactic antibiotics) scheduled during the study;
15. Unable to discontinue drugs that are specifically used as antiperistaltic agents (e.g., intended to control diarrhea, including but not limited to loperamide, diphenoxylate-atropine, or opioids);
    a) NOTE: Opioids prescribed for chronic pain or other indications are allowed if stable dose or decreasing dose during the course of the study. Changes in regimen should be discussed with the Medical Monitor;
16. Active drug, chemical, or alcohol dependency as determined by the Investigator through history or optional toxicology screen;
17. Enrollment in any other investigational drug or device study within 30 days prior to Randomization (Day 1) or within 5 half-lives of the last dose of the previous investigational compound, whichever is longer;
18. Pregnant, breast-feeding, or considering becoming pregnant during the study;
19. Clinically significant abnormal laboratory values including, but not limited to, white blood cell count $\geq 15 \times 10^9$ laboratory evidence of acute kidney injury, or absolute neutrophil count of $< 1\times 10^9$ neutrophils at Screening; or
20. Any acute or chronic medical comorbidity, psychiatric, social, or other circumstances that, in the opinion of the Investigator, may interfere with study compliance, completion, or accurate assessment of study outcomes/safety.

NOTE: To be eligible for Randomization, the above listed Inclusion/Exclusion Criteria as well as the following <u>additional</u> Inclusion Criteria must be satisfied:

Randomization (Day 1) Inclusion Criteria:

1. An outpatient prior to Randomization;
   a) NOTE: Subject may be enrolled while an inpatient in an acute care facility, but must be discharged prior to Randomization on Day 1. Subjects residing in an assisted living center, long-term care facility, or rehabilitation center may be randomized;
2. Has received a course of standard-of-care CDI antibiotics for the most recent CDI episode (for 10-42 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator);
3. Has an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during standard-of-care CDI antibiotics prior to Randomization; and
4. [redacted]

Test Product, Dose, and Mode of Administration:

The active ingredient of CP101, [redacted], is derived from the stools of normal healthy donors who are highly screened, tested, and monitored in a clinically structured donation program. [redacted] Eligible subjects will be allocated to 1 of 2 treatment groups in a 1:1 ratio:

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NA = Not applicable.

Duration of Treatment:

[redacted], including active drug (CP101) and placebo; subjects will be monitored through Week 24 following Randomization.

Criteria for Evaluation:

Efficacy: Clinical signs and symptoms of recurrent CDI, including frequency and consistency of stools, will be confirmed by a *C. difficile* stool testing algorithm, as described above. North American Pulse-field type 1 (NAP1)/BI/027 subtyping will be performed if symptoms are consistent with recurrent CDI. [redacted], stool will be assessed for ARB, [redacted] An overview of evaluations to be performed is outlined in the Schedule of Observations (Table 1.a).

Safety: Safety will be assessed via adverse event monitoring, concomitant medication use, physical examinations, vital signs, electrocardiograms, clinical laboratory safety analyses, and pregnancy testing (if female is of childbearing potential).

Statistical Methods:

For the primary efficacy endpoint, the proportion of subjects with sustained clinical cure, defined as absence of recurrent CDI through Week 8, will be tested using a Chi-Square test for treatment group differences. The primary efficacy analysis will be conducted for the Intent-to-Treat (ITT), modified ITT (mITT), and Per-Protocol (PP) populations. [redacted]

Endpoints:

Primary Endpoints:

- Proportion of subjects experiencing sustained clinical cure, defined as absence of recurrent CDI, through Week 8, and
- Incidence of adverse events through Week 8

Secondary Endpoints:

The secondary endpoints are:

- Proportion of subjects experiencing recurrent CDI with ribosomal NAP1/BI/027 *C. difficile* subtype through Week 8;
- Time-to-first recurrent CDI episode during the study (Day 1 through Week 8);
- Proportion of subjects experiencing sustained clinical cure at Week 24;
- Time-to-first recurrent CDI episode during the study (Day 1 through Week 24);
- Incidence of hospitalization due to recurrent CDI through Week 8 and through Week 24;
- Incidence of decolonization of ARB, defined as vancomycin-resistant enterococci, extended-spectrum ß-lactamase organisms, or carbapenem-resistant Enterobacteriaceae at Week 8 and Week 24 among co-colonized subjects;
- [redacted]
- Change in body mass index (BMI) by Week 8 and Week 24 relative to medically documented pre-CDI BMI; and
- [redacted]

Other Safety Endpoint:

The other safety endpoint is:

- Incidence of adverse events through Week 24.

[redacted]

Table 1.a Schedule of Observations

Study time point/ activities	Week	Screening[1]	Rand. Visit[2]	Efficacy and Safety Assessment Period						Safety and CDI Recurrence Follow-Up Period			
		Prior to study drug (On-site)	0 (On-site)	1 (Tel)	2 (Tel)	3 (Tel)	4 (On-site)	7 (Tel)	8 (On-site)	11 (Tel)	12 (Tel)	23 (Tel)	Week 24 or early termination visit[3] (On-site)
	Day		1	7 ± 2	14 ± 2	21 ± 2	28 ± 3	49 ± 3	56 ± 3	77 ± 3	84 ± 7	161 ± 7	168 ± 14
Screening/Administrative Assessments													
Informed consent[4]		X											
Inclusion/Exclusion Criteria		X	X[5]										
Demographics		X											
Medical history (including BMI)[6]		X											
Memory Aid data recording[7, 8]		X	X	X	<———				(X)				———>
Memory Aid distribution, training, and/or review[8]		X	X	X	<———				(X)				———>
Telephone contact[9]		X[1]		X	X	X		X		X	X	X	
Randomization[10]			X[5]										
Start/continue treatment of standard-of-care CDI antibiotics[11]		X											
[redacted]		X	X[5,12]						X				X
Study drug administration			X[13]										
Safety Assessments													
Complete physical examination[14]			X[5]										
Symptom-directed physical examination[8,15]		X					X		X				X
Vital signs[8,16], height[17], and weight[8,18]		X	X[19]				X		X				X
12-lead ECG (per standard-of-care)[20]		X							X				X[20]
Clinical safety laboratory evaluations[21]		X	X[5]				X		X				X
Drug screen (as needed)[22]		X											
Pregnancy testing[23]		X	X[5]						X				X
Concomitant medications[8]		X	X[5]	<———					X				———>
Adverse events[8,24]		X	X	<———					X				———>
Stool Assessments													
Stool sample collection[8]		X	X[5]	(X)	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	X
Bristol Stool Scale[8]		X	X[5]	X	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	X
[redacted]		X	X[5]	(X)	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	X
Assessment for ARB[8,26]		X	X[5]	(X)	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	X
NAP1/BI/027 subtyping[8]				(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
C. difficile stool testing algorithm[8]				(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)

ARB = antibiotic-resistant bacteria; BMI = body mass index; C. difficile = Clostridium difficile; CDI = Clostridium difficile infection; ECG = electrocardiogram; GI = gastrointestinal; hCG = human chorionic gonadotropin; NAP1 = North American Pulse-field type 1; rand. = randomization; RNA = ribonucleic acid; Tel = telephone assessment.
(X) = in the event of suspected recurrent CDI

1 The Screening visit includes the entire Screening period up to the time of Randomization. The Screening period is limited to 60 days between the signing of informed consent and Randomization. Where referenced as the Screening visit, study-required tests and procedures may be performed on 1 day or across multiple days, but preferably closest to the time of Randomization. During the Screening visit, potential study subjects will be fully informed regarding the nature of the study and possible adverse events, and will receive a copy of the informed consent form for review. All subjects must have a stool specimen documented as testing positive for *C. difficile* performed at the site or local laboratory within the previous 60 days from Randomization. After the Screening visit, 1 phone call will be made to the subject as a reminder for the upcoming Randomization visit.
In the event that the Screening period is planned for > 30 days, additional clinical safety laboratory evaluations may be conducted at the discretion of the Investigator.

2 [redacted] If the subject experiences diarrhea for 2 or more consecutive days during the washout period, the Investigator should contact the Medical Monitor.

3 If a subject discontinues from the study early, the subject will be asked to return to the clinic within 14 days after discontinuation to undergo the Week 24 assessments prior to study discharge. All other subjects will have their final visit at Week 24 ± 14 days.

4 The signing of the informed consent form initiates the screening process. Obtain signed, written informed consent and permission to use Protected Health Information (in accordance with the Health Insurance Portability and Accountability Act). Informed consent must be in place prior to performing any study procedures.

5 To be performed prior to study drug administration. NOTE: Missing stool sample does not preclude the subject from Randomization.

6 Includes CDI history (e.g., number of prior episodes) and a pre-CDI medically documented weight or BMI will be obtained.

7 Subjects will be issued a paper Memory Aid at the time of informed consent and given training on its use. The Memory Aid data will be discussed at the Screening visit and Randomization visit (Day 1) after drug administration. At Week 1 telephone call, the Memory Aid data will be discussed and subjects will be reminded to bring it to the Week 4 visit.

8 To be performed in the event of a suspected CDI recurrence at the timepoints marked as (X). For stool sample, instructions for at-home stool sample collection, handling, storage, and transportation/shipping are included in the Laboratory Manual and an instruction sheet will be distributed to subjects.

9. Subjects will be contacted by telephone. Subjects will be asked about any adverse events, including occurrence of diarrhea. If a subject reports diarrhea, the study staff will review the timing of those episodes and the subject may be asked to submit a stool sample for *C. difficile* testing. Subjects will be asked about their general well-being, changes in their health status, medications, and over-the-counter remedies, and will be reminded about their next study visit. From Screening through study completion, subjects will be reminded to record all relevant information on their Memory Aid, as applicable. If a solicitated adverse event is Grade 2 or greater on telephone contact at Week 1, an unscheduled visit will be arranged as soon as possible for evaluation and confirmation of the event. For all subsequent telephone contacts adverse events will be managed according to good clinical practice at the discretion of the treating physician.
At Week 4, 8, 24 visits every effort will be made to conduct an on-site assessment. However, under extenuating subject circumstances that make an on-site visit not feasible and after all reasonable measures to enable the subject's on-site visit have been exhausted, a telephone assessment will be conducted.

10 Randomization will occur [redacted]. Eligible subjects will be allocated to 1 of 2 treatment groups in a 1:1 ratio.

11 For the most recent CDI episode, the subject will have received standard-of-care CDI antibiotics (10-42 days; with exact duration, antibiotic type, and dose at the discretion of the Investigator).

12 [redacted]

13 Subjects will have completed a mandatory washout [redacted] Study drug will be administered under direct supervision of clinic staff as an oral dose ([redacted]. Subjects will remain in the clinic for observation for at least 1 hour post-dose.

14 A complete physical examination will be performed (including evaluation of general appearance/mental status; head, eyes, ears, nose, throat; and the following body systems: skin, heart, lungs, abdomen, and extremities).

15 The Investigator will perform symptom-directed physical examinations based on subjects' signs and symptoms.

16 Vital signs (blood pressure, heart rate, and temperature) will be measured per standard-of-care. Body temperature should be taken at all visits where vital signs are measured. Vital signs and body temperature should also be measured at time of recurrence, if any.

17 Height will be measured at the Screening visit only per standard-of-care.

18 Subjects should be weighed per standard-of-care. Height and weight will be used to calculate BMI. BMI will be calculated from weight collected at Week 8 and Week 24 as well.

19 Vital signs will be measured before and after (within 60 minutes) study drug administration.

20 Single 12-lead ECG will be performed per standard-of-care at Screening and at Week 8. Evidence of clinically significant abnormalities during the Screening visit may result in exclusion from the study. At Week 24, the 12-lead ECG will be performed only if there are findings at the Week 8 ECG, or if the subject has symptoms requiring an ECG.

21 [redacted]

22 Optional (at the discretion of the Investigator) drug screen includes cotinine (not exclusionary), amphetamines, barbiturates, benzodiazepines, cannabinoids (not exclusionary), cocaine, opiates (not exclusionary), and alcohol.

23 Women of childbearing potential enrolled in this study will have serum hCG pregnancy testing administered during Screening and urine pregnancy testing thereafter, at the discretion of the Investigator. Women who are post-menopausal for ≥ 1 year or surgically sterile will not undergo pregnancy testing.

24 The adverse event reporting period will begin with informed consent and will continue through study completion or, in the case of withdrawal, until the outcome is determined. Adverse events will be collected after study drug administration on Day 1. Subjects will be asked about any adverse events, including occurrence of diarrhea. If a subject reports diarrhea, the study staff will review the timing of those episodes and the subject may be asked to submit a stool sample for *C. difficile* testing. Subjects will be asked about their general well-being, changes in their health status, medications, and over-the-counter remedies.

25 [redacted]

26 Stool sample collection for the assessment for ARB, defined as vancomycin-resistant enterococci, extended-spectrum ß-lactamase organisms, or carbapenem-resistant Enterobacteriaceae, will be performed on samples obtained at Screening, Randomization (Day 1) prior to study drug administration, Week 8, and Week 24. Assessment for ARB may also be performed at any other visit or time point (e.g., time of recurrence, if any).

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4.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ARB	Antibiotic-resistant bacteria
BMI	Body mass index
BSS	Bristol Stool Scale
C. difficile	*Clostridium difficile*
CDI	*Clostridium difficile* infection
CFR	Code of Federal Regulations
CI	Confidence interval
CRA	Clinical Research Associate
CRE	Carbapenem-resistant Enterobacteriaceae
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
ESBL	Extended-spectrum ß-lactamase
FDA	Food and Drug Administration
FMT	Fecal microbiota transplantation
FSM®	Full-Spectrum Microbiota®
GCP	Good Clinical Practice
GI	Gastrointestinal
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-Treat
MDSEC	Multidrug-sensitive *Escherichia coli*
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NAP1	North American Pulse-field type 1
NCI	National Cancer Institute

PP	Per-Protocol
PPI	Proton pump inhibitors
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
UTI	Urinary tract infection
VRE	Vancomycin-resistant enterococci
WHO	World Health Organization

5.0 INTRODUCTION

5.1 Background Information on *Clostridium difficile* Colitis

Clostridium difficile (*C. difficile)* colitis or pseudomembranous colitis is a colitis (inflammation of the large intestine) resulting from infection with *C. difficile*, a spore-forming bacterium. It causes an infectious diarrhea called *C. difficile*-associated diarrhea. Latent symptoms of *C. difficile* infection (CDI) often mimic some flu-like symptoms and may mimic disease flare-ups in people with inflammatory bowel disease (IBD)-associated colitis. *C. difficile* releases toxins that may cause bloating and diarrhea with abdominal pain, which may become severe.

CDI is a disease that is increasing in incidence and severity in the United States. [1] In a review from the National Hospital Discharge Survey, CDI incidence increased from 4.5 per 1,000 total adult discharges in 2001 to 8.2 per 1,000 total adult discharges in 2010. [2] The infections remain primarily healthcare-related but are seen more and more in the community setting. In 2011, *C. difficile* was estimated to be responsible for approximately 500,000 infections and 29,000 deaths. [3] The rate of severe CDI disease is also increasing, including CDI caused by strains such as ribotype 027 that produces a third toxin, or binary toxin, and shows resistance to fluoroquinolone antibiotics. There is evidence that infection with 027 is a significant risk factor for relapse. [4] This strain is more prevalent in healthcare institutions than in community-based infection cases (30.7% versus 18.8% in healthcare institutions and in community-based cases, respectively, $p < 0.001$).

Patients with recurrent CDI may initially respond to treatment with oral vancomycin or metronidazole. The recurrence of CDI symptoms can be caused by germination of residual *C. difficile* spores or acquisition of a new CDI. Diarrhea often recurs within days to weeks after antibiotics are stopped, in part because the antibiotics themselves destabilize the microbial community structure of the distal gut. Fidaxomicin, introduced in 2011, [5] offers an alternative antibiotic treatment and is included in the American College of Gastroenterology guidelines for mild-to-moderate disease.

5.2 Fecal Microbiota Transplantation for *Clostridium difficile* Colitis

Fecal microbiota transplantation (FMT), also known as fecal bacteriotherapy, has been used since the late 1950's to treat patients with recurrent CDI who are unresponsive to antibiotic therapy. FMT has been used even longer in the veterinary field. A randomized trial comparing duodenal infusion administration of FMT showed superiority to vancomycin therapy in treating recurrent CDI. [6] Published clinical case studies and series [7,8] have expanded these data and show that FMT has high efficacy (85-100%) by a variety of gastrointestinal (GI) routes for treating patients with recurrent CDI. Routes of administration include retention enema, colonoscopic delivery, and nasogastric or nasojejunal tube. These findings have been detailed in updated reviews. [9,10] Use of FMT achieved similar results in a cohort of immunocompromised patients, [11] with few serious adverse events (SAEs), or procedure- or microbiota-related adverse events, including no related infectious complications. A study comparing a 10-day course of vancomycin followed by a pulse regimen with the same antibiotic, versus a 3-day course of vancomycin followed by FMT with stool by colonoscopy resulted in 18 of 20 patients treated resolving *C. difficile*-related diarrhea. This was in contrast to 5 of 19 patients on the

vancomycin-only protocol. Neither group had any SAEs, further supporting the safety of FMT versus antibiotic therapy. [12]

These findings have led to the evolution of FMT as the recommended treatment approach in patients with 2 or more CDI relapses. The 2013 American College of Gastroenterology and 2014 European Society of Clinical Microbiology and Infectious Diseases (Strength of Recommendation: A, Quality of Evidence: I) list FMT as a treatment option for relapsing CDI failing vancomycin taper. [13,14] [redacted]

5.3 Product Summary and Rationale

The Sponsor is focusing on developing FMT into a mainstream oral treatment for recurrent CDI.

[redacted] Having a stable, oral formulation could eliminate the need to perform colonoscopy, enema, or other invasive GI procedures to deliver the transplant in most of the target recurrent CDI population.

5.4 Experience with Full-Spectrum Microbiota®

[redacted]

Table 5.a List of Clinical Experience with FSM® for Recurrent CDI

Formulation	Clinic	No. of Patients	Dose Range	Route of Administration	GMP Product	Success Rate	
						1 FMT	Overall [1]
Lyophilized	University of Minnesota, MN (Staley, 2017 [15])	49	2.1×10^{11} to 2.5×10^{12}	Oral capsule	No	89.7%	87.8%

1. Success rates for patients with 1 or more FMTs.

CDI = *Clostridium difficile* infection; FMT = fecal microbiota transplantation; FSM® = Full-Spectrum Microbiota®; GMP = Good Manufacturing Practice; No. = number.

5.4.1 FSM®, Lyophilized Formulation

5.4.1.1

Table 5.b [redacted]

[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

5.4.1.1.1 [redacted]

[redacted]

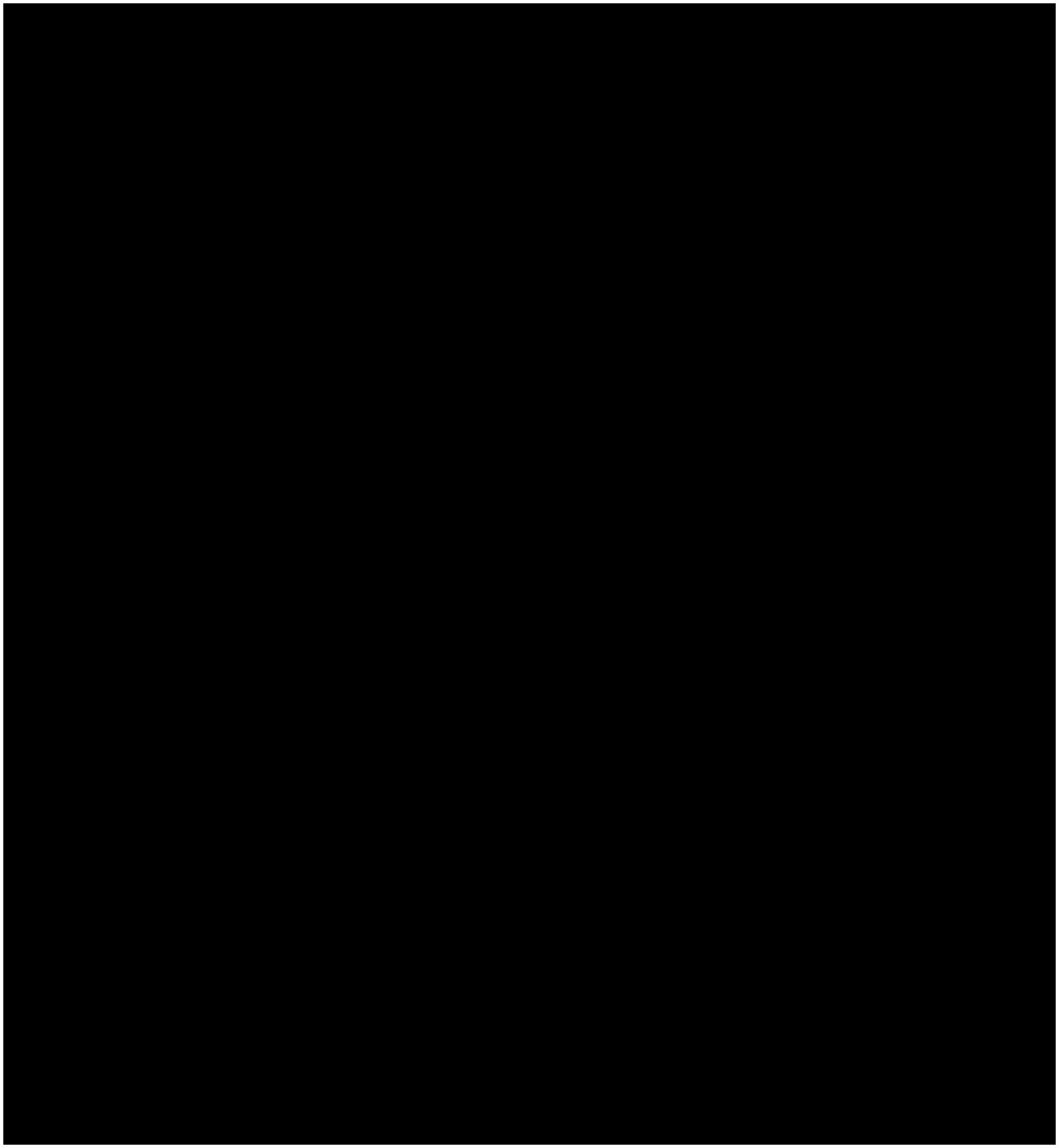

Table 5.c [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]

[redacted]

[redacted]

5.4.2 Clinical Safety of FSM®, Frozen and Lyophilized

[redacted]

5.4.3 Potential Risks and Benefits

[redacted]

5.4.4 Dose Selection

[redacted]

6.0 STUDY OBJECTIVES

The objectives of this Phase 2 study are:

- To evaluate the safety and tolerability of CP101 treatment compared to placebo in adults with previously treated recurrent CDI.
- To evaluate the efficacy of CP101 treatment relative to placebo in adults with previously treated recurrent CDI.

7.0 INVESTIGATIONAL PLAN

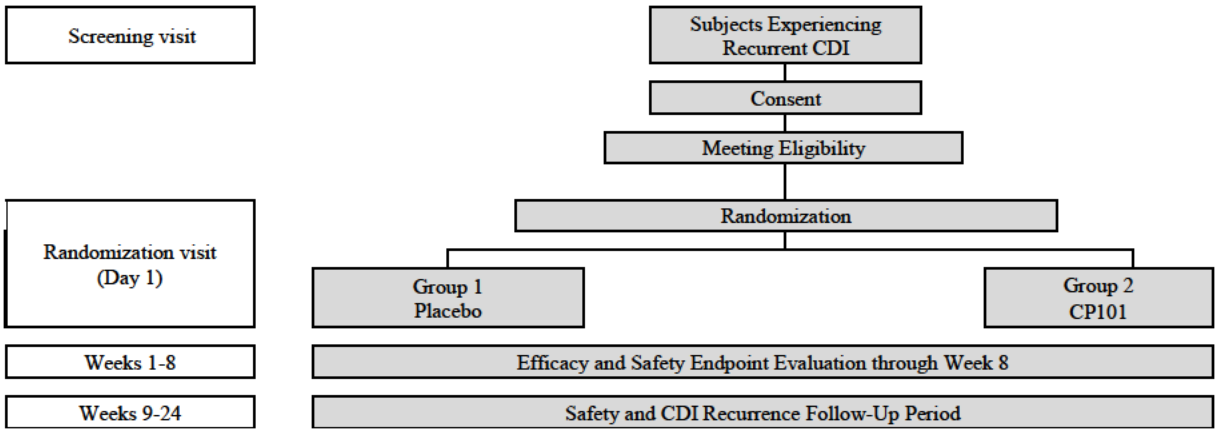
7.1 Overall Study Design

This is a double-blind, placebo-controlled, parallel-arm, multicenter study comparing the safety, tolerability, and efficacy of CP101 treatment relative to placebo in adults with previously treated recurrent CDI. Subjects who are experiencing recurrent CDI will undergo screening procedures. Subjects who meet eligibility criteria will be randomized to study drug.

[redacted] Subjects will be monitored for recurrence of CDI, safety, and tolerability for 24 weeks following Randomization. The primary efficacy and safety endpoints will be evaluated at 8 weeks post-treatment, and all subjects will continue to be followed for an additional 16 weeks for safety and recurrence of CDI.

To qualify for the study, subjects must be experiencing recurrent CDI defined as: a) ≥ 3 episodes of CDI, with 2 episodes occurring within the previous 12 months (inclusive of the current episode); OR b) 2 episodes of CDI occurring within the previous 6 months (inclusive of the current episode) AND 65 years of age or older. Additionally, to qualify, recurrent CDI subjects must have received standard-of-care CDI antibiotics for the most recent CDI episode (for 10-42 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator) and have an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during standard-of-care CDI antibiotics prior to Randomization.

Figure 7.a Study Design



CDI = *Clostridium difficile* infection.

The primary clinical outcome is recurrence of CDI and is defined as a) diarrhea (> 3 unformed stools [Bristol Stool Scale (BSS) score of 6 or 7] per day) for 2 or more consecutive days; b) a stool specimen testing positive for *C. difficile* by a testing algorithm (see Figure 10.a); and c) requiring a course of standard-of-care CDI antibiotics. Secondary outcomes include assessment of decolonization of antibiotic-resistant bacteria (ARB) and [redacted]

[redacted]

Subjects will be issued a paper Memory Aid at the time of informed consent (Section 10.2) and given training on its use in order to aid in capturing the following information: occurrence of GI symptoms, frequency of stools, fecal urgency, stool incontinence, BSS, and any new medications taken (including antibiotics for treatment of CDI). Subjects will return the Memory Aid to the clinic and will review it with the coordinator at the Screening visit and Randomization (Day 1) after drug administration. At Week 1 telephone call, the Memory Aid data will be discussed, and subjects will be reminded to bring it to the Week 4 visit. In the event of suspected CDI recurrence, the Memory Aid recorded after Week 1 will be discussed at unscheduled visit(s).

Clinical signs and symptoms of recurrent CDI, including frequency and consistency of stools, will be confirmed by a *C. difficile* stool testing algorithm (see Figure 10.a). North American Pulse-field type 1 (NAP1)/BI/027 subtyping will be performed if symptoms are consistent with recurrent CDI. [redacted], stool will be assessed for ARB, and [redacted]. An overview of evaluations to be performed is outlined in the Schedule of Observations (Table 1.a).

Safety will be assessed via adverse event monitoring, concomitant medication use, physical examinations, vital signs, electrocardiograms (ECGs), clinical safety laboratory evaluations, and pregnancy testing (if female is of childbearing potential).

[redacted]

If a subject discontinues from the study early, the subject will be asked to return to the clinic within 14 days after discontinuation to undergo the scheduled Week 24 assessments prior to study discharge. All other subjects will have their final visit at Week 24 ± 14 days.

7.2 Study Sites

[redacted]

7.3 Duration of Study

The study duration will be approximately 24 weeks following Randomization visit, including an 8-week Efficacy and Safety Assessment Period and an additional 16-week safety and CDI Recurrence Follow-up Period.

7.4 Criteria for Study Termination

The study will be completed as planned unless any of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study;
- [redacted]
- Significant violation of International Council for Harmonisation (ICH) Good Clinical Practice (GCP) that compromises the ability to achieve the study objectives or compromises subject safety; and
- Sponsor decision.

Should the study be terminated, all relevant study documentation and study drug must be returned to the Sponsor.

8.0 SELECTION AND WITHDRAWAL OF SUBJECTS

Study eligibility will be evaluated during the Screening visit, which will take place prior to the Randomization visit (Day 1).

8.1 Inclusion Criteria

1. Ability to provide written informed consent;
2. Men or women 18 years of age or older;
3. Recurrent CDI* as defined by:
   a) ≥ 3 episodes of CDI, with 2 episodes occurring within the previous 12 months (inclusive of the current episode); OR
   b) 2 episodes of CDI occurring within the previous 6 months (inclusive of the current episode) AND 65 years of age or older;

   *NOTE: CDI is defined by:
   a) History of diarrhea (≥ 3 unformed stools per day) for 2 or more consecutive days; AND
   b) A stool specimen documented as testing positive for *C. difficile* within 60 days prior to Randomization. Testing for CDI may include:
      i. [redacted]

      AND
   c) Has received a course of standard-of-care CDI antibiotics for the most recent CDI episode (for 10-42 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator); and AND
   d) Has an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during standard-of-care CDI antibiotics prior to Randomization;
4. Willingness to abstain from consuming non-dietary probiotics through Week 8 after Randomization;
5. Women must fulfill at least 1 of the following criteria:
   a) Post-menopausal, defined as amenorrhea ≥ 1 year;
   b) Surgically sterile: hysterectomy, bilateral oophorectomy, or tubal ligation; or

c) Abstinent or willing to use adequate contraception from Screening through the Week 24 visit, per Section 11.2; and

6. Deemed to have life expectancy of 8 weeks or greater.

8.2 Exclusion Criteria

1. Admitted to, or expected to be admitted to, an intensive care unit for any medical reason;
   a) NOTE: Residents of long term care facilities, such as nursing homes and rehabilitation centers, are eligible for study entry;
   b) NOTE: Patient visits to clinics, urgent care centers, acute care hospitals, or emergency departments are allowed; however, subject must be an outpatient prior to Randomization;
2. Stools known to be positive for ova and/or parasite(s), or other enteric pathogens (e.g., *Salmonella*, *Shigella*, and/or *Campylobacter*) within 28 days prior to Screening;
3. Inability to ingest capsules (e.g., severe nausea, vomiting, and/or dysphagia);
4. Known or suspected toxic megacolon and/or known small bowel ileus;
5. Prior history, evidence, or diagnosis of inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, indeterminate colitis, or microscopic colitis);
6. Recent diagnosis (< 6 months prior to Screening) of diarrhea-predominant irritable bowel syndrome (post-infection or not related to an enteric infection). Subjects with diarrhea-predominant irritable bowel syndrome ≥ 6 months prior to Screening may be randomized after consultation with the Medical Monitor;
7. Current diagnosis of chronic diarrheal illness with pre-CDI baseline diarrhea (≥ 3 loose stools in a 24-hour period). This includes but is not limited to celiac disease, bile salt diarrhea, chronic pancreatitis, and short gut syndrome;
8. Past administration of bezlotoxumab (Zinplava™), or past enrollment in a *C. difficile* vaccine study within 12 months of Randomization;
9. Initiation of any systemic cancer treatment (e.g. chemotherapy, radiotherapy, biologic, others) for active malignancy that is planned 8 weeks prior to Randomization or during the 8 weeks following Randomization. Subjects on maintenance treatment for malignancy may be randomized after consultation with the Medical Monitor.
10. Initiation or escalation of immunosuppressive agents, at the discretion of the Investigator, for any condition during the 8 weeks prior to Randomization or planned during the 8 weeks following Randomization. Subjects on stable immunosuppressive agents or short-courses may be randomized after consultation with the Medical Monitor. NOTE: Solid organ transplant recipients are excluded;
11. Compromised immune system, including, but not limited to, a known history of human immunodeficiency virus infection and a cluster of differentiation 4 count that is unknown or documented to be < 200 cells/mm^3 within the last year, or an acquired immunodeficiency syndrome-defining illness; or at the discretion of the Investigator;

12. Fecal transplant for any condition, regardless of route of administration in the last year or plans to undergo during the study;
13. Major intra-abdominal surgery (e.g., bowel resection) within the past 60 days prior to Screening (excluding appendectomy or cholecystectomy), history of total colectomy/ileostomy and/or planned invasive surgery/hospitalization during the study;
    a) NOTE: Subjects with history of bariatric surgery may be randomized after consultation with the Medical Monitor;
14. Use of a systemic antibiotic for any condition (other than CDI therapy for the current recurrence) during the Screening period, or any anticipated use of a systemic antibiotic for any condition other than CDI during the study for 8 weeks after Randomization. This includes subjects who have a known medical procedure that requires antibiotic prophylaxis (e.g., elective surgical procedure or dental procedure requiring prophylactic antibiotics) scheduled during the study;
15. Unable to discontinue drugs that are specifically used as antiperistaltic agents (e.g., intended to control diarrhea, including but not limited to loperamide, diphenoxylate-atropine, or opioids);
    a) NOTE: Opioids prescribed for chronic pain or other indications are allowed if stable dose or decreasing dose during the course of the study. Changes in regimen should be discussed with the Medical Monitor;
16. Active drug, chemical, or alcohol dependency as determined by the Investigator through history or optional toxicology screen;
17. Enrollment in any other investigational drug or device study within 30 days prior to Randomization (Day 1) or within 5 half-lives of the last dose of the previous investigational compound, whichever is longer;
18. Pregnant, breast-feeding, or considering becoming pregnant during the study;
19. Clinically significant abnormal laboratory values including, but not limited to, white blood cell count $\geq 15 \times 10^9$, laboratory evidence of acute kidney injury, or absolute neutrophil count of $< 1 \times 10^9$ neutrophils at Screening; or
20. Any acute or chronic medical comorbidity, psychiatric, social, or other circumstances that, in the opinion of the Investigator, may interfere with study compliance, completion, or accurate assessment of study outcomes/safety.

NOTE: To be eligible for Randomization, the above listed Inclusion/Exclusion Criteria as well as the following <u>additional</u> Inclusion Criteria must be satisfied:

8.3 Randomization (Day 1) Inclusion Criteria

1. An outpatient prior to Randomization;
    a) NOTE: Subject may be enrolled while an inpatient in an acute care facility, but must be discharged prior to Randomization on Day 1. Subjects residing in an assisted living center, long-term care facility, or rehabilitation center may be randomized;

2. Has received a course of standard-of-care CDI antibiotics for the most recent CDI episode (for 10-42 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator);
3. Has an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during standard-of-care CDI antibiotics prior to Randomization; and
4. Subject has completed a washout [redacted]

8.4 Reasons for Study Discontinuation

All subjects will be free to discontinue study participation at any point during the study, for any reason, and without prejudice to their further medical care. In addition, the Investigator can discontinue a subject from the study at any time. Subjects will be encouraged to remain in the study through Week 24, regardless of the occurrence of adverse events, study outcome, or Week 8 results.

The primary reason for a subject's withdrawal should be recorded in the subject's source record and on the electronic case report form (eCRF) using 1 of the following categories:

- Adverse event: The subject experiences an adverse event that impacts the safety of continued participation in this study or the subject is unwilling to continue because of an adverse event.
- Subject voluntary withdrawal.
- Investigator withdrawal of subject.
- Lost to follow-up: In the case of subjects lost to follow-up, attempts to contact the subject must be made and documented in the subject's medical records.
- Study termination: The Sponsor, DSMC, IRB/IEC, or regulatory agency terminates the study.
- Other: Any other reasons, based upon the medical judgment of the Investigator and discussion with the Medical Monitor.

If a subject discontinues from the study early, the subject will be asked to return to the clinic within 14 days after discontinuation to undergo the scheduled Week 24 assessments prior to study discharge.

Discontinued or withdrawn subjects will not be replaced.

8.5 Subject Identification and Number Assignment

At Screening, site personnel will use interactive response technology (IRT) to register the subject. A subject identification number in the format of XXX-XXXX will be generated in IRT, and will be used to identify the subject throughout the study, including subject transfer to another site. This number will be entered on all documentation. A subject identification number will not be assigned to more than 1 subject. If a subject is not eligible to receive treatment, or if a subject

discontinues from the study, the subject identification number cannot be assigned to another subject.

9.0 TREATMENTS

9.1.1 Description of Study Drug

9.1.1.1 CP101

[redacted]

9.1.1.2 Placebo

Because this is a double-blind, placebo-controlled study, placebo will be presented in capsules that are identical in size, smell, texture, and appearance to those of the CP101 capsules.

9.1.2 Dose and Regimen of Study Drug

Each subject who qualifies for Randomization will be randomly assigned to 1 of 2 treatment arms in a 1:1 allocation ratio (CP101 or placebo; Table 9.a) in accordance with the randomization schedule.

Table 9.a Treatments Administered

[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NA = Not applicable.

Study drug will be administered as an oral dose under the direct supervision of clinic staff after Randomization on Day 1, [redacted]

Dosing instructions:

- Take study drug (CP101 or placebo) dose [redacted]) orally [redacted]; and
- [redacted]

Subjects will remain in the clinic for observation for at least 1 hour post-dose.

9.1.3 Dosage Form, Manufacturing, Packaging, and Labeling of Study Drug

CP101 and placebo will be formulated as capsules for oral administration. The study sites will be supplied with study drug in a double-blind manner (i.e., placebo capsules will be identical in size, smell, texture, and appearance to CP101 capsules).

[redacted]

Refer to the Pharmacy Manual for additional information.

9.1.4 Storage of Study Drug

[redacted]

Refer to the Pharmacy Manual for additional information.

9.1.5 Method of Randomizing Subjects to Study Drug

The unblinded study biostatistician will create the randomization schedule which will be uploaded in the IRT for implementation. Subjects who satisfy the randomization eligibility criteria will be randomized in a 1:1 ratio to receive CP101 or placebo via the IRT. There is no stratification to be used in the randomization. The Investigator or the Investigator's designee will enter all screening information, including demographics, and will confirm Inclusion/Exclusion Criteria in order to obtain the subject randomization number and a corresponding bottle number for treatment assignment.

9.1.6 Study Drug Blinding

The study drug blind will be maintained through Week 8. Subjects, the Sponsor, Investigators, and all study site personnel involved with the study, carrying out study procedures, evaluating subjects, entering study data, and/or evaluating study data will remain blinded to treatment allocations until all subjects have completed the Week 8 assessments and the database has been locked for the analysis at Week 8. The Investigators, study site personnel, and subjects will remain blinded until Week 24.

Active and placebo product will be identical with the exception of a unique identification number on the bottle label.

9.1.7 Study Drug Unblinding

Investigators shall not break the study blind during the study, and Investigators should treat all subjects as if they had received CP101. However, in situations in which knowledge of the subject's study drug is necessary for clinical management, the Investigator must first attempt to

contact the Medical Monitor or designee (contact information is on the Signature Page of this document), to discuss and agree to the need for unblinding to occur. The Medical Monitor or designee will answer calls 24 hours a day, 7 days a week, and 365 days of the year. In situations in which the Investigator has tried, but is unable to reach the Medical Monitor or designee, he/she should use best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the Medical Monitor or designee.

Once a subject's treatment assignment has been unblinded, the Medical Monitor and study coordinator should be notified within 24 hours of unblinding of the treatment. Information relating to unblinding (e.g., date and time of the call to the Medical Monitor by the Investigator, reason for unblinding, and date and time of unblinding) shall be clearly recorded in the subject's study file and in the electronic data capture (EDC) system, as part of relevant standard operating procedures. In addition, the Investigator should consider whether the clinical event prompting unblinding should be considered an adverse event or SAE, according to the regulatory definitions or criteria for adverse events or SAEs, and if so, submit an adverse event/SAE report to Sponsor or designee (see Section 11.0).

Sponsor or designee will also unblind any SAE reports that are unexpected, and considered to be related to the study drug, in accordance with safety reporting guidance and regulations.

9.1.8 Study Drug Accountability Procedures

Responsibility for study drug accountability at the study site rests with the Investigator; however, the Investigator may delegate applicable study drug accountability duties to an appropriately trained pharmacist or designee. Inventory and accountability records must be maintained and must be readily available for inspection by the CRA and are open to inspection at any time by any applicable regulatory authorities.

The Investigator or designee will be expected to collect and retain all used, unused, and partially used study drug bottles. The Investigator or designee must maintain records that document the following:

- Study drug delivery to the study site,
- Shipping conditions upon arrival,
- Inventory at the study site,
- Storage conditions at the study site,
- Bottle number assigned to each subject, and
- [redacted]

These records should include dates, quantities, and batch/serial numbers (if available).

The study drug must be used only in accordance with the protocol.

Prior to study site closure or at appropriate monitoring intervals, a representative from the Sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the Sponsor or its designee. The Investigator will retain the original documentation regarding clinical study material accountability as well as clinical study material return and/or destruction, and copies will be sent to the Sponsor.

9.1.9 Antibiotic Therapy

Subjects who present with a current recurrent CDI episode during Screening, defined as: a) ≥ 3 episodes of CDI, with 2 episodes occurring within the previous 12 months (inclusive of the current episode); OR b) 2 episodes of CDI occurring within the previous 6 months (inclusive of the current episode) AND 65 years of age or older will be evaluated for inclusion in the study. To qualify, recurrent CDI subjects must have received standard-of-care CDI antibiotics for the most recent CDI episode (for 10-42 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator) and have an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during standard-of-care CDI antibiotics prior to Randomization.

9.1.10 Concomitant Therapy and Restricted Medications

[redacted]

9.1.11 Diet

[redacted]

10.0 ASSESSMENT OF EFFICACY

The primary clinical outcome of recurrent CDI is defined as a) diarrhea (> 3 unformed stools [BSS score of 6 or 7] per day) for 2 or more consecutive days; b) a stool specimen testing positive for *C. difficile* by a testing algorithm (see Figure 10.a); and c) requiring a course of standard-of-care CDI antibiotics. NAP1/BI/027 subtyping will be performed if symptoms are consistent with recurrent CDI. [redacted] will be evaluated and stool will be assessed for ARB and [redacted] at multiple time points.

10.1 Stool Sample Analyses

Stool samples will be collected and analyzed as shown in the Schedule of Observations (Table 1.a).

A stool specimen documented as testing positive for *C. difficile* by local testing performed at the site or local laboratory is required within the 60 days prior to Randomization for inclusion in the study. Subjects will be excluded if there is known testing on stool specimens known to be positive for ova and/or parasite(s), or other enteric pathogens (e.g., *Salmonella*, *Shigella*, and/or *Campylobacter*) within 28 days prior to Screening.

Further stool samples will be collected at Screening while the subject is completing a course of standard-of-care CDI antibiotics for the most recent CDI episode or during a washout period [redacted] prior to Randomization and at Randomization prior to study drug administration. [redacted], assessment for ARB (Section 10.1.3), and safety testing.

[redacted]

In the event that CDI recurrence is suspected, stool samples will also be used for NAP1/BI/027 subtyping, as well as testing for CDI using a *C. difficile* testing algorithm (see Figure 10.a and Section 10.1.4).

Complete instructions for collection, handling, storage, and transportation/shipping of stool samples will be provided in a separate Laboratory Manual.

10.1.1 Bristol Stool Scale

Stool samples will be collected at Screening while the subject is completing a course of standard-of-care CDI antibiotics for the most recent CDI episode or during the washout period, at Randomization (Day 1) prior to study drug administration, Week 8 visit, Week 24 visit, and at any time there is a suspected CDI recurrence up to Week 24, as described in Section 10.1. All samples will be described using the 7-point BSS (Table 10.a). The BSS score will be recorded and reviewed by the Investigator.

Table 10.a Bristol Stool Scale

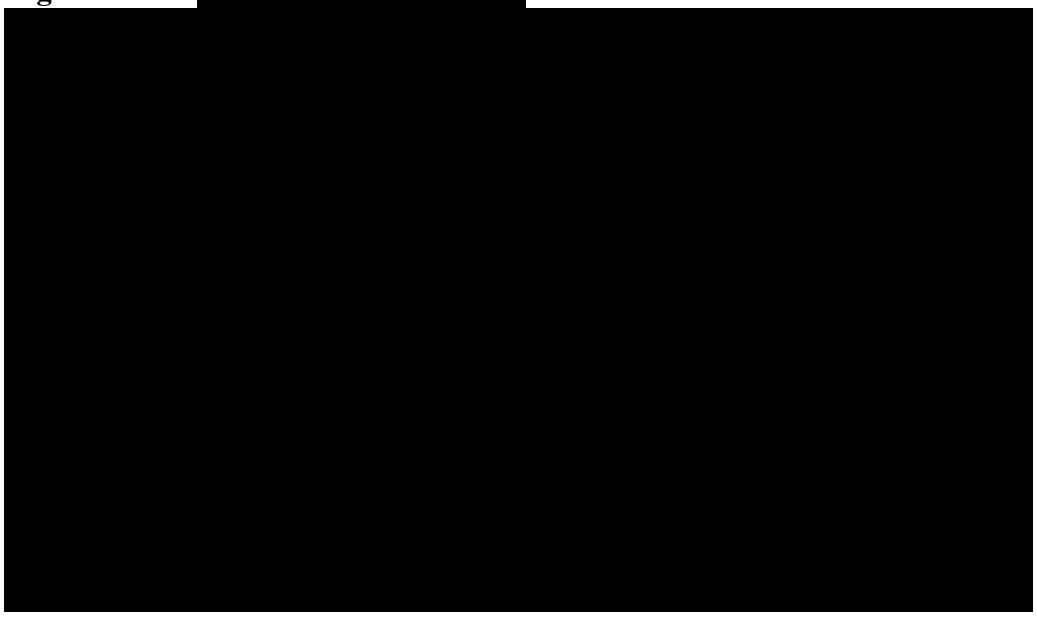
10.1.2

10.1.3 Assessment for Antibiotic-Resistant Bacteria

Stool sample collection for the assessment for ARB, defined as vancomycin-resistant enterococci (VRE), extended-spectrum ß-lactamase organisms (ESBL), or carbapenem-resistant Enterobacteriaceae (CRE), will be performed on samples obtained at Screening, Randomization (Day 1) prior to study drug administration, Week 8, and Week 24. Assessment for ARB may also be performed at any other visit or time point (e.g., time of recurrence, if any).

10.1.4

Figure 10.a [redacted]



10.2 Subject Memory Aid

Subjects will be issued a Memory Aid at the time of informed consent and given training on its use. The Memory Aid will be discussed at the Screening Visit, Randomization (Day 1) after drug administration. At the Week 1 telephone call, the Memory Aid data will be discussed, and subjects will be reminded to bring it to the Week 4 visit. In the event of suspected CDI recurrence, the Memory Aid recorded after Week 1 will be discussed at unscheduled visit(s). Subjects will use the Memory Aid to assist in obtaining the following information as detailed in Table 10.b:

- Occurrence (see Table 10.b) of GI symptoms, including: abdominal cramping, abdominal pain, abdominal tenderness, nausea, dehydration, bloating, poor appetite, unformed stools, vomiting, blood or pus in stool, stool incontinence, and fecal urgency;
- Frequency of stools;
- Recording of temperature, if the subject detects a fever;
- BSS for each stool recorded; and
- Any new medications taken (over-the-counter and prescription; including antibiotics for treatment of CDI).

The study site staff will review the Memory Aid with the subject and obtain clarification if needed. The study staff will enter the data in the eCRF, as applicable. The Investigator may be required to review and document their interpretation of the BSS responses, in combination with the reported GI symptoms, in order to make informed data-reporting decisions. If the Memory Aid is not returned to the clinic, the subject can contact study site staff during the Follow-up Period to report the above information. Study staff will add a source note to document the collected data as needed. If a solicitated adverse event is Grade 2 or greater during the telephone contact at Week 1, an unscheduled visit will be arranged as soon as possible for evaluation and confirmation of the event. For all subsequent telephone contacts, adverse events will be managed according to good clinical practice at the discretion of the treating physician.

The solicited signs and symptoms will be entered in the eCRF. All solicited adverse events will not only be entered in the eCRF but also analyzed in the final study report, along with other safety analyses, and reported in an expedited manner if they meet the regulatory definition of a serious and unexpected suspected adverse reaction.

Table 10.b Solicited Adverse Event Severity Grading Table

Event	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-Threatening)
Abdominal cramping/pain/ tenderness	Transient discomfort over baseline causing no or minimal interference with ADL	Marked discomfort over baseline causing greater than minimal interference with ADL, but still acceptable	Incapacitating discomfort over baseline causing considerable interference with ADL; unacceptable	Disabling pain causing inability to perform basic activities
Nausea	Transient symptoms over baseline causing loss of appetite without alternation in eating habits	Marked symptoms over baseline; oral intake decreased without significant weight loss, dehydration or malnutrition	Incapacitating symptoms over baseline; inadequate oral caloric or fluid intake, tube feeding, TPN. or hospitalization indicated	NA
Dehydration	Increased oral fluid indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated < 24 hours	IV fluids or hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Bloating	Transient symptoms over baseline causing no or minimal interference with ADL	Marked symptoms over baseline causing greater than minimal interference with ADL, but still acceptable	Incapacitating symptoms over baseline causing considerable interference with ADL; unacceptable	NA
Poor appetite (e.g., anorexia)	Loss of appetite without alteration of eating habits compared to baseline	Oral intake altered without significant weight loss or malnutrition; oral nutrition supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated
Unformed stool (BSS score of 6 or 7)	Increase of ≤ 3 stools over baseline in 24 hours	Increase of 4-6 stools over baseline in 24 hours	Bloody diarrhea, if not present at baseline; increase of ≥ 7 stools over baseline in 24 hours; OR IV fluid replacement indicated	Life-threatening symptoms and/or consequences (e.g., hypotensive shock)
Vomiting	1-2 episodes (separated by 5 minutes) in 24 hours	3-5 episodes (separated by 5 minutes) in 24 hours	≥ 6 episodes (separated by 5 minutes) in 24 hours; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Blood or pus in stool	Asymptomatic or mild symptoms compared to baseline; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms compared to baseline; minimal, local, or non-invasive interventions indicated; limiting age-appropriate instrumental ADL	Severe or medically significant symptoms compared to baseline but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Stool incontinence	Transient symptoms over baseline; occasional use of pads required	Marked symptoms over baseline; daily use of pads required	Severe symptoms over baseline; elective operative intervention indicated	NA
Fecal urgency	Transient symptoms over baseline causing no or minimal interference with ADL	Marked symptoms over baseline causing greater than minimal interference with ADL, but still acceptable	Incapacitating symptoms over baseline causing considerable interference with ADL; unacceptable	NA

Fever	38.0-39.0°C (100.4-102.2°F)	> 39.0-40.0°C (102.3-104.0°F)	> 40.0°C (> 104.0°F) for ≤ 24 hours	> 40.0°C (> 104.0°F) for > 24 hours

ADL = activities of daily living; BSS = Bristol Stool Scale; IV = intravenous; NA = not applicable;
TPN = total parenteral nutrition.
Source: Adapted from the National Cancer Institute Common Terminology Criteria for Adverse Events (Version 4.03)

10.2.1 Gastrointestinal Symptoms and Medications

The presence of any GI symptoms should be captured with the assistance of the Memory Aid Any new medications will be recorded (name/type, dose, frequency, and reason for taking).

10.2.2 Unformed Stools and Diarrhea Assessments

The primary clinical outcome of recurrent CDI is defined as a) diarrhea (> 3 unformed stools [BSS score of 6 or 7] per day) for 2 or more consecutive days; b) a stool specimen testing positive for *C. difficile* by a testing algorithm (see Figure 10.a); and c) requiring a course of standard-of-care CDI antibiotics. Testing for CDI will be as described in Section 10.1.4.

If a subject has diarrhea (> 3 unformed stools [BSS score of 6 or 7] per day) for 2 or more consecutive days) accompanied by confirmation of CDI by a *C. difficile* testing algorithm, and received additional CDI standard-of-care therapy, then diarrhea will not be recorded as an adverse event; instead, it will be considered an on-study recurrent CDI episode and will be included in the determination of efficacy (Section 13.5).

The occurrence and frequency of stools and occurrence of urgency and stool incontinence will be assessed from Screening through completion of the Week 1 telephone visit.

In addition, subjects are to report diarrhea (as defined above) promptly to the study coordinator at any time during the study. The study coordinator will then instruct the subject on when he/she should return to the clinic and whether a stool sample should be collected based on the signs and symptoms.

11.0 ASSESSMENT OF SAFETY

11.1 Adverse Events

The adverse event reporting period will begin with informed consent and will continue through study completion or, in the case of withdrawal, until the outcome is determined. Adverse events will be assessed at each visit and through telephone contact with the subject. A neutral question, such as "How have you been feeling since your last visit?" may be asked. The term "adverse event" could include any of the following events that develop or increase in severity during the course of the study:

1. Any signs or symptoms, regardless of severity, and whether or not ascribed to the study drug;
2. Any clinically significant laboratory abnormality; or
3. Any abnormality detected during physical examination.

Any laboratory abnormalities deemed clinically significant by the Investigator must be reported as an adverse event. A clinically significant abnormality is a confirmed abnormality (by repeat test) that is changed sufficiently from baseline so that, in the judgment of the Investigator, a change in management is warranted. This alteration may include: monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment. If the abnormal laboratory test is part of a known syndrome or disease, the syndrome/disease, and not the individual laboratory test, should be recorded as the adverse event.

The primary clinical outcome of recurrent CDI is defined as a) diarrhea (> 3 unformed stools [BSS score of 6 or 7] per day) for 2 or more consecutive days; b) a stool specimen testing positive for *C. difficile* by a testing algorithm (see Figure 10.a); and c) requiring a course of standard--of-care CDI antibiotics. If a subject has diarrhea for 2 or more consecutive days accompanied by confirmation of *C. difficile* as described above, and received additional CDI standard-of-care therapy, then diarrhea will not be recorded as an adverse event; instead, it will be considered an on -study recurrent CDI episode and will be included in the determination of efficacy (Section 13.5).

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events, if the condition(s) is (are) known before the start of the study drug dosing. In the latter case, the condition should be reported as medical history.

The Clinical Investigator will follow all subjects withdrawn from the study due to any adverse event until the outcome is determined and where appropriate, additional written reports will be provided.

The intensity of an adverse event will be graded according to the scale below in addition to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) for Grading the Severity of Adult Adverse Events. The clinical significance of the adverse event is determined by the Investigator. The Investigator is encouraged to consult with the Medical Monitor, as needed, to discuss the case.

Grade	Description
Grade 1 (Mild):	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 (Moderate):	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3 (Severe):	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4 (Life-Threatening):	Life-threatening consequences; urgent intervention indicated
Grade 5 (Death):	Death related to adverse event

When the intensity of an adverse event changes over time for a reporting period (e.g., between visits), each change in intensity will be reported as an adverse event until the event resolves. For example, 2 separate adverse events will be reported if a subject experiences Grade 1 headache for 3 days, meeting the definition of an adverse event, and then after 3 days the event increases to a Grade 3 intensity that lasts for 2 days and then resolves. The Grade 1 event will be reported as an adverse event with a start date equal to the day the event met the adverse event definition and a stop date equal to the day that the event increased in intensity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an adverse event with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date on the day that the event changed intensity again or resolved. For analysis purposes, this will be considered a single adverse event for this subject and only the maximum intensity will be recorded.

The relationship of each adverse event to study drug or study intervention will be defined using the terms below.

No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-
    - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
    - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant drug-
  - The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug-
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug-
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

11.1.1 Serious Adverse Events

SAEs are defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening (the term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability and/or incapacity;
- Results in a congenital anomaly and/or birth defect; or
- Is any important medical event, based on medical and scientific judgment, which may not be immediately life-threatening or result in death or hospitalization, but may pose substantial risks to the subject or may require medical intervention to prevent 1 of the other outcomes listed in the definition above.

Another definition of SAE that should be classified and reported as such for this protocol includes:

- Suspected transmission of an infectious agent (e.g., any pathogenic organism, virus, or infectious particle) via the study drug.

The following hospitalizations or situations will <u>not</u> be considered or reported as SAEs in this study unless an unpredicted complication results in prolonged hospitalization:

- Visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or the event is life--threatening);
- Elective surgery, planned prior to signing consent (recorded on Medical History);
- Admission for a planned medical/surgical procedure prior to signing consent (recorded on Medical History);

- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy);
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases;
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative); and
- A suspected clinical endpoint event, regardless of when the event occurs, should not be reported as an adverse event. A suspected clinical endpoint event includes recurrent CDI.

11.1.1.1 Serious Adverse Event Reporting

All SAEs and pregnancies occurring while the subject is in the study or within 30 days after the subject received their study dose must be reported within 24 hours of the knowledge of the event, whether or not considered to be related to study drug.

All SAEs should be reported after the subject signs the informed consent and followed until resolution, stabilization, or until the Investigator provides sufficient evidence that no further information can be obtained.

[redacted]

Although not all information required for a complete SAE form may be readily available at the time of the event, the Investigator must include sufficient information on the SAE form to allow for a complete medical assessment. This should include at a minimum the subject number, study site number, detailed description of the event, seriousness criteria, intensity, and causality/relationship to study drug.

After submission of the initial report, the Investigator will provide follow-up information to [redacted] as requested (e.g., concomitant medications and hospital discharge summary) to further evaluate the event and assure that all appropriate information is received. Once all information is received and the SAE has been deemed appropriate for closure, the SAE form must be signed and dated by the Investigator within the adverse event eCRF.

The Investigator will be responsible for informing the IRB/IEC of the SAE in accordance with institutional policies and procedures including relevant initial and follow-up information about the SAE.

11.1.1.2 [redacted]

[redacted]

11.2 Contraception Requirements and Pregnancy

11.2.1 Contraception Requirements

All women of childbearing potential must practice effective contraception from Screening through the Week 24 visit. For the purposes of this study, women who do not meet 1 of the criteria listed below for non-childbearing potential are considered to be physiologically capable of becoming pregnant and are, therefore, defined as women of childbearing potential:

- Criteria for non-childbearing potential:
    - Post-menopausal: defined as amenorrhea ≥ 1 year, or
    - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy, or
    - Hysterectomy, or
    - Bilateral tubal ligation.

If a female subject does not fulfill post-menopausal or surgically sterile criteria, the subject must be abstinent or willing to practice effective contraception from Screening through the Week 24 visit. For the purposes of the study, highly effective contraception is defined as:

- Combination of an established form of hormonal contraception (oral, injected, or implanted) or an intrauterine device or intrauterine system;

And at least 1 of the following:

- A physical barrier method of contraception with use of a spermicide such as condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide, unless not available in a country;
- Male vasectomy with negative semen analysis documentation. The use of contraception does not apply if the male partner has been vasectomized at least 6 months before dosing; and/or
- Complete abstinence may be considered an acceptable method of contraception at the discretion of the Investigator. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

The combination of 2 barrier methods, periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods), and withdrawal are not considered acceptable methods of contraception.

11.2.2 Pregnancy

Although pregnancy is not always considered an adverse event or SAE by regulatory definition, for this study, pregnancies must be handled as SAEs for data transmission purposes. In the event that a pregnancy complication occurs or elective termination of a pregnancy is required for medical reasons, then the complication will be recorded as an adverse event or SAE as appropriate.

While elective and uncomplicated induced abortion not required for medical reasons does not constitute an adverse event or SAE (even if the subject is hospitalized to undergo abortion), spontaneous abortion is considered a fatal event and must be reported as an adverse event and SAE as appropriate.

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an adverse event or, if appropriate, as an SAE. A spontaneous abortion is always considered an SAE and should be reported as described in the SAE Reporting section (Section 11.1.1.1).

Women of childbearing potential enrolled in this study will have serum human chorionic gonadotropin (hCG) pregnancy testing administered during Screening and urine pregnancy testing thereafter. Women who are post-menopausal for ≥ 1 year or surgically sterile will not undergo pregnancy testing.

Any pregnancy and/or suspected pregnancy that occurs during the study in a female subject should be reported. Any pregnancy and/or suspected pregnancy will be followed for outcome.

The Investigator must notify the Sponsor immediately after the pregnancy is confirmed. If the subject has received the study drug prior to becoming pregnant, the subject will continue the efficacy assessment and follow-up periods, and measures of safety and efficacy will be obtained.

The subject will be followed until the outcome of the pregnancy is determined. It is the responsibility of the Investigator to obtain and document pregnancy information on the most

recent Pregnancy Report Form. Furthermore, any SAE occurring as outcome of the pregnancy must be reported to the Medical Monitor.

11.3 Vital Signs, Height, and Weight

Vital signs (blood pressure, heart rate, and temperature) will be assessed per standard-of-care as listed in the Schedule of Observations (Table 1.a). Vital signs will be measured before and after (within 60 minutes) study drug administration. Body temperature should be taken at all visits where vital signs are measured. Vital signs and body temperature should also be measured at time of recurrence, if any.

Body weight and height (Screening only) will be measured per standard-of-care. Height and weight will be used to calculate body mass index (BMI). A pre-CDI medically documented weight or BMI will be obtained. BMI will be calculated from weight collected at Week 8 and Week 24 as well.

11.4 Physical Examinations

A complete physical examination (including evaluation of general appearance/mental status; head, eyes, ears, nose, throat; and the following body systems: skin, heart, lungs, abdomen, and extremities) will be performed at the time points listed in the Schedule of Observations (Table 1.a).

The Investigator will perform the symptom-directed physical examinations based on subjects' signs and symptoms at the time points listed in the Schedule of Observations (Table 1.a).

11.5 Electrocardiograms

Single 12-lead ECGs will be performed per standard-of-care at the time points listed in the Schedule of Observations (Table 1.a). Evidence of clinically significant abnormalities during the Screening visit may result in exclusion from the study. A 12-lead ECG will only be performed at Week 24 if there are findings at the Week 8 ECG or if the subject has symptoms requiring an ECG.

11.6 Clinical Safety Laboratory Evaluations

Samples of blood and urine are scheduled for collection at Screening, at Randomization (Day 1) prior to study drug administration, and at Weeks 4, 8, and 24; specific tests performed at each visit are shown in Table 11.a. In the event that the Screening period is planned for > 30 days, additional clinical safety laboratory evaluations may be conducted at the discretion of the Investigator.

The total volume of blood collected at scheduled study visits will be approximately 123 mL. Additional follow-up samples for clinical laboratory testing should be obtained as clinically indicated. A 3-mL serum aliquot will be collected at each time point and archived for safety testing as may be required by emergence of adverse conditions.

Subjects with a white blood cell count $\geq 15 \times 10^9$, laboratory evidence of acute kidney injury, or an absolute neutrophil count of $< 1 \times 10^9$ neutrophils at Screening are to be excluded from the study.

All clinical laboratory testing, with the exception of optional drug testing or on-site urine pregnancy testing during the treatment period for females of childbearing potential, will be performed by the central clinical laboratory.

Table 11.a Clinical Laboratory Safety Tests

Category	Analyte
Hematology	Complete blood count with differential.
Chemistry	[redacted]
Coagulation	Activated partial thromboplastin time, prothrombin time, and international normalized ratio.
Urinalysis	[redacted]
Screening only	
Drug Screen (Optional, at discretion of the Investigator)	Optional drug screen including cotinine (not exclusionary), amphetamines, barbiturates, benzodiazepines, cannabinoids (not exclusionary), cocaine, opiates (not exclusionary), and alcohol.
Pregnancy	Serum hCG for women of childbearing potential.

hCG = human chorionic gonadotropin.

12.0 STUDY PROCEDURES BY VISIT

Subjects who provide informed consent and meet all the eligibility criteria for participation in this study will be enrolled. To qualify for this study, subjects must be experiencing recurrent CDI as defined in Section 7.1.

The study consists of a Screening Period, an 8-week Efficacy and Safety Assessment Period, followed by an additional 16-week Safety and CDI Recurrence Follow-Up Period. Overall, subjects will be monitored for 24 weeks after the Randomization visit.

Stool samples will be collected before or after each scheduled clinic visit. Subjects may also be asked to bring a stool sample for unscheduled visits. Instructions for collection, handling, storage, and transportation/shipping are included in the Laboratory Manual.

12.1 Study Visits Description

12.1.1 Screening (On-site Visit)

The Screening period is limited to [redacted]. Where referenced as the Screening visit, study-required tests and procedures may be performed on [redacted], but preferably [redacted]. In the event that the Screening period is planned for [redacted], additional clinical safety laboratory evaluations may be conducted at the discretion of the Investigator.

During the Screening visit, potential study subjects will be fully informed regarding the nature of the study and possible adverse events, and will receive a copy of the informed consent form (ICF) for review. Potential study subjects must read the ICF and sign the document after the Investigator or designee has answered all questions to the study candidate's satisfaction, with further procedures only proceeding after the ICF has been signed. The original signed ICF will be retained by the Investigator and a copy will be given to the subject.

Study candidates will be evaluated for study entry according to the Inclusion/Exclusion Criteria (Sections 8.1 and 8.2). The Investigator will evaluate the results of all examinations, including clinical laboratory tests and stool sample analyses, and will determine each candidate's suitability for the study. [redacted]. The following procedures will be performed at Screening:

- Obtain signed, written informed consent and permission to use Protected Health Information (in accordance with the Health Insurance Portability and Accountability Act [HIPAA]) (see Section 15.5 for consent requirements). Refusal to provide this permission excludes an individual from eligibility for study participation. Record the date informed consent was given and who conducted the process on the appropriate source documentation. Informed consent must be in place prior to performing any study procedures.
- Determine study eligibility through review of the Inclusion/Exclusion Criteria (see Sections 8.1 and 8.2).
- A stool specimen documented as testing positive for *C. difficile* performed at the site or local laboratory is required within the 60 days prior to Randomization for inclusion in the study. Subjects will be excluded if there is known testing on stool specimens known to be

positive for ova and/or parasite(s), or other enteric pathogens (e.g., *Salmonella*, *Shigella*, and/or *Campylobacter*) within 28 days prior to Screening.

- Obtain demographics and medical history, including:
  - Number of prior episodes of CDI; and
  - A pre-CDI medically documented weight or BMI.
- Distribute paper Memory Aid and provide training on proper use. Record patient status at the time of informed consent and collect.
- Start/continue treatment of standard-of-care CDI antibiotics for the most recent CDI episode (10-42 days; with exact duration, antibiotic type, and dose at the discretion of the Investigator).
- [redacted]
- Perform a symptom-directed physical examination based on subjects' signs and symptoms.
- Collect vital signs, height, and weight per standard-of-care.
- Perform 12-lead ECG per standard-of-care.
- Obtain blood and urine samples for clinical laboratory safety testing and optional drug screen.
- Obtain a blood sample from all women of childbearing potential for pregnancy testing, at the discretion of the Investigator.
- Inquire about concomitant medications and adverse events.
- Collect stool sample while the subject is completing a course of standard-of-care CDI antibiotics for the most recent CDI episode. Samples will undergo BSS stool assessment (Section 10.1.1) and will be used for fecal microbiome analysis, including, but not limited to, [redacted] assessment for ARB (Section 10.1.3), and safety testing.
- After the Screening visit, perform a follow-up phone call 1 time as a reminder for the upcoming Randomization visit.

12.1.2 Randomization (Day 1; On-site Visit)

Prior to study drug administration:

- [redacted]
- [redacted]
- Perform a complete physical examination.
- Per standard-of-care, collect weight and vital signs within 60 minutes prior to study drug administration.
- Obtain blood and urine samples for clinical laboratory safety testing.

- Obtain urine sample from all women of childbearing potential for pregnancy testing at the discretion of the Investigator.
- Inquire about concomitant medications since the last visit.
- Collect stool sample following a washout [redacted]
- [redacted], if the subject meets all Inclusion Criteria and none of the Exclusion Criteria (Section 8.3), conduct randomization to 1 of 2 treatment groups in a 1:1 ratio.

Study drug administration:

- Subjects will have completed a mandatory washout [redacted]. Under direct supervision of clinic staff, administer blinded study drug ([redacted].

[redacted]

12.1.3 Week 1 (Telephone Contact)

- Perform follow-up phone call including a reminder for the next visit.
- Review Memory Aid data with the subject.
- Inquire about concomitant medications and adverse events since the last visit. If a solicitated adverse event Grade 2 or greater is reported, an unscheduled clinic visit will be arranged as soon as possible for evaluation and confirmation of event.
- In the event that CDI recurrence is suspected, conduct the unscheduled visit procedures as detailed in Section 12.1.13.

12.1.4 Week 2 and Week 3 (Telephone Contact)

- Perform follow-up phone call including a reminder for the next visit.
- Review Memory Aid data with the subject, as applicable.
- Inquire about concomitant medications and adverse events since the last visit.

- In the event that CDI recurrence is suspected, conduct the unscheduled visit procedures as detailed in Section 12.1.13.
- Remind subject to bring Week 1 Memory Aid to Week 4 visit.

12.1.5 Week 4 (On-site Visit)

Note: Every effort will be made to conduct an on-site assessment at Week 4. However, under extenuating subject circumstances that make an on-site visit not feasible and after all reasonable measures to enable the subject's on-site visit have been exhausted, a telephone assessment will be conducted.

- Perform a symptom-directed physical examination based on subjects' signs and symptoms.
- Collect vital signs and weight per standard-of-care.
- Obtain blood and urine samples for clinical laboratory safety testing.
- Inquire about concomitant medications and adverse events since the last visit.
- In the event that CDI recurrence is suspected, conduct the unscheduled visit procedures as detailed in Section 12.1.13.
- Collect Week 1 Memory Aid.

12.1.6 Week 7 (Telephone Contact)

- Perform follow-up phone call including a reminder for the next visit.
- Review Memory Aid data with the subject, as applicable.
- Inquire about concomitant medications and adverse events since the last visit.
- In the event that CDI recurrence is suspected, conduct the unscheduled visit procedures as detailed in Section 12.1.13.

12.1.7 Week 8 (On-site Visit)

Note: Every effort will be made to conduct an on-site assessment at Week 8. However, under extenuating subject circumstances that make an on-site visit not feasible and after all reasonable measures to enable the subject's on-site visit have been exhausted, a telephone assessment will be conducted.

- [redacted]
- Review Memory Aid data with the subject, as applicable.
- Perform a symptom-directed physical examination based on subjects' signs and symptoms.
- Collect vital signs and weight per standard-of-care.
- Perform 12-lead ECG per standard-of-care.
- Obtain blood and urine samples for clinical laboratory safety testing.
- Obtain urine sample from all women of childbearing potential for pregnancy testing.

- Inquire about concomitant medications and adverse events since the last visit.
- [redacted]
- In the event that CDI recurrence is suspected, conduct the unscheduled visit procedures as detailed in Section 12.1.13.

12.1.8 Week 11 (Telephone Contact)

- Perform follow-up phone call including a reminder for the next visit.
- Review Memory Aid data with the subject, as applicable.
- Inquire about concomitant medications and adverse events since the last visit.
- In the event that CDI recurrence is suspected, conduct the unscheduled visit procedures as detailed in Section 12.1.13.

12.1.9 Week 12 (Telephone Contact)

- Perform follow-up phone call including a reminder for the next visit.
- Review Memory Aid data with the subject, as applicable.
- Inquire about concomitant medications and adverse events since the last visit.
- In the event that CDI recurrence is suspected, conduct the unscheduled visit procedures as detailed in Section 12.1.13.

12.1.10 Week 23 (Telephone Contact)

- Perform follow-up phone call including a reminder for the next visit.
- Review Memory Aid data with the subject, as applicable.
- Inquire about concomitant medications and adverse events since the last visit.
- In the event that CDI recurrence is suspected, conduct the unscheduled visit procedures as detailed in Section 12.1.13.

12.1.11 Week 24/Early Termination Visit (On-site Visit)

Note: Every effort will be made to conduct an on-site assessment at Week 24/Early Termination. However, under extenuating subject circumstances that make an on-site visit not feasible and after all reasonable measures to enable the subject's on-site visit have been exhausted, a telephone assessment will be conducted.

- [redacted]
- [redacted]
- Perform a symptom-directed physical examination based on subjects' signs and symptoms.
- Collect vital signs and weight per standard-of-care.

- Perform a symptom-driven 12-lead ECG per standard-of-care. If there are findings at the Week 8 ECG or if the subject is experiencing symptoms requiring an ECG, the Week 24 ECG is mandatory as a follow-up.
- Obtain blood and urine samples for clinical laboratory safety testing.
- Obtain urine sample from all women of childbearing potential for pregnancy testing, at the discretion of the Investigator.
- Inquire about concomitant medications and adverse events since the last visit.
- Collect stool sample. Samples will undergo [redacted] assessment for ARB (Section 10.1.3), and safety testing. [redacted]
- In the event that CDI recurrence is suspected, conduct the unscheduled visit procedures as detailed in Section 12.1.13.

12.1.12 Routine Telephone Follow-Up

Subjects will be contacted by telephone as described above and in the Schedule of Observations (Table 1.a). Subjects will be asked about any adverse events, including occurrence of diarrhea. If a subject reports diarrhea, the study staff will review the timing of those episodes and the subject may be asked to submit a stool sample for *C. difficile* testing (Figure 10.a). Subjects will be asked about their general well-being, changes in their health status, medications, and over-the-counter remedies and will be reminded about their next study visit. From Screening through study completion, subjects will be reminded to record all relevant information on their Memory Aid, as applicable. Note: At Week 4, 8, 24 visits every effort will be made to conduct an on-site assessment. However, under extenuating subject circumstances that make an on-site visit not feasible and after all reasonable measures to enable the subject's on-site visit have been exhausted, a telephone assessment will be conducted.

12.1.13 Unscheduled Visit for Suspected Recurrence of CDI

Subjects are to report diarrhea promptly to the study coordinator at any time during the study. Any subject with diarrhea (> 3 unformed stools [BSS score of 6 or 7] per day) for 2 or more consecutive days must collect a stool sample and return with this sample to the clinic for an unscheduled visit.

- Collect stool sample. Samples will undergo [redacted] assessment for ARB (Section 10.1.3), and safety testing. Perform NAP1/BI/027 subtyping if symptoms are consistent with recurrent CDI.
- [redacted]
- Collect Memory Aid, resupply subject with a new Memory Aid, and review.
- Inquire about concomitant medications and adverse events since the last visit.
- Perform a symptom-directed physical examination based on subjects' signs and symptoms.
- Collect vital signs and weight per standard-of-care.

- Assess subject for signs and symptoms of CDI recurrence.
- Perform laboratory testing, as clinically indicated, including testing stool for CDI using a *C. difficile* testing algorithm (see Figure 10.a).
- [redacted]

13.0 STATISTICAL METHODS

13.1 Study Endpoints

13.1.1 Primary Endpoints

The primary endpoints are:

- Proportion of subjects experiencing sustained clinical cure, defined as absence of recurrent CDI, through Week 8, and
- Incidence of adverse events through Week 8.

13.1.2 Secondary Endpoints

The secondary endpoints are:

- Proportion of subjects experiencing recurrent CDI with ribosomal NAP1/BI/027 *C. difficile* subtype through Week 8;
- Time-to-first recurrent CDI episode during the study (Day 1 through Week 8);
- Proportion of subjects experiencing sustained clinical cure at Week 24;
- Time-to-first recurrent CDI episode during the study (Day 1 through Week 24);
- Incidence of hospitalization due to recurrent CDI through Week 8 and through Week 24;
- Incidence of decolonization of ARB, defined as VRE, ESBL organisms, or CRE at Week 8 and Week 24 among co-colonized subjects;
- [redacted]
- Change in BMI by Week 8 and Week 24 relative to medically documented pre-CDI BMI; and
- Incidence of newly diagnosed autoimmune disease through Week 8 and Week 24.

13.1.3 Other Safety Endpoint

The other safety endpoint is:

- Incidence of adverse events through Week 24.

13.1.4 [redacted]

- [redacted]

13.2 Overview

Descriptive statistical methods will be used to summarize study data, with hypothesis testing performed for the primary efficacy endpoints at Week 8. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation, minimum, and maximum for continuous data, and refers to frequencies and percentages for categorical data. For some data that may be presented as continuous variables, there may be scientific reasons to present those data in constructed categories as well (e.g., BMI). Reasons for

the categories will be described in the Clinical Study Report. Graphical displays may be presented for selected results.

A stand-alone Statistical Analysis Plan (SAP) will be written to describe in detail all statistical analyses planned for the study. It will be accompanied by mock Tables, Figures, and Listings. The SAP will be finalized and approved by signatures and dates prior to database lock for Week 8. The SAP will take precedence over the protocol for details about the statistical analyses for the study. In addition to the SAP, other graphical representations of the results may be produced after review of the data (post-hoc).

Verbatim terms recorded for medical history conditions, surgical history procedures, and adverse events will be mapped to an SOC and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), and all prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

13.3 Analysis Populations

Four analysis populations are planned for the study:

Intent-to-Treat population (ITT or All Randomized)	All subjects randomized into the study. The ITT population will be analyzed according to the treatment group to which subjects were randomized.
The modified ITT population (mITT or Full Analysis population)	All subjects in the ITT population who receive at least 1 capsule of study drug at Randomization (Day 1). The mITT population will be the primary analysis population for all efficacy analyses.
Per-Protocol population (PP population)	All subjects in the mITT population who have not violated key Inclusion/Exclusion Criteria, Randomization Criteria, and/or have not had a major protocol deviation in a way that could influence the efficacy assessment.
Safety population	All enrolled subjects who received at least 1 capsule of study drug. Unless otherwise stated, the Safety population will be the default analysis population for all safety analyses. Analyses of safety will be performed based on treatment received, even if different from the treatment group to which subjects were randomized.

13.4 Subject Disposition

Subject disposition will be presented for all subjects. The number of subjects who are randomized, treated, complete the study, and discontinue from the study will be provided. The reasons for early discontinuation will also be presented. These tables and listings will be presented for data through Week 8 and then cumulative through Week 24. Differences in study disposition between Week 8 and Week 24 will be explored by characterizing the subject demographics, treatment group, and subsequent outcomes.

13.5 Efficacy Analysis

13.5.1 Primary Endpoints

For the primary efficacy endpoint, the proportion of subjects with sustained clinical cure, defined as absence of recurrent CDI through Week 8, will be tested using a Chi-Square test for treatment group differences. The primary efficacy analysis will be conducted for the ITT, mITT, and PP populations, as defined in Section 13.3. The mITT population will be the primary analysis population for all efficacy analyses.

For the primary efficacy analysis, the active treatment group will be compared to the placebo group. The null hypothesis will be tested at a p-value < 0.05.

> Null Hypothesis: There is no difference between the proportion of subjects with sustained clinical cure, defined as absence of recurrent CDI through Week 8, in the CP101 group compared to the placebo group.

Sensitivity analyses of the primary efficacy outcome in the mITT population and PP population will also be conducted in the active treatment group versus placebo group using Chi-Square tests. Further details regarding sensitivity analyses will be discussed in the SAP.

13.5.2 Secondary [redacted] Endpoints

All comparisons of the secondary endpoints will be performed at a 2-sided 0.05 significance level, and no corrections for multiple testing will be made.

- The proportion of subjects experiencing recurrent CDI through Week 8 in each treatment group will be stratified by ribosomal NAP1/BI/027 *C. difficile* subtype and compared using Fisher's exact test for group and subtype differences.
- The time-to-first on-study CDI recurrence and associated 95% confidence interval (CI) will be estimated using the Kaplan-Meier method by treatment group through Week 8.
- Proportion of subjects experiencing sustained clinical cure at Week 24.
- The time-to-first on-study CDI recurrence and associated 95% CI will be estimated using the Kaplan-Meier method by treatment group through Week 24.
- Incidence rate and 95% CIs will be used to test for treatment differences for incidence of hospitalization due to recurrent CDI through Week 8 and then through Week 24.
- Incidence rate and 95% CIs will be used to test for treatment differences for incidence of decolonization of ARB, defined as VRE, ESBL organisms, or CRE at Week 8 and Week 24 among co-colonized subjects.
- [redacted]
- Change in BMI by Week 8 and Week 24 relative to medically documented pre-CDI BMI.
- Incidence rate and 95% CIs will be constructed for any newly diagnosed autoimmune disease for the study population, presented by treatment group through Week 8 and Week 24.

[redacted]

13.6 Safety Analysis

All safety data will be presented in subject listings.

For the primary safety endpoint, the incidence rate will be presented by treatment group for adverse events reported through Week 8.

For the other safety endpoint, the incidence rate will be presented by treatment group for adverse events reported through Week 24.

Adverse events will be tabulated by MedDRA SOC and preferred term. The occurrence of TEAEs will be summarized by treatment group using MedDRA SOCs, preferred terms, and severity.

All adverse events will be listed for individual subjects showing both verbatim and preferred terms. Separate summaries of treatment-emergent SAEs and TEAEs related to study drug will be generated.

Any event reported on the eCRF that occurs on or after the initiation of study drug is defined as treatment-emergent. Additionally, it will be assumed that an adverse event that was reported to have started at Randomization (Day 1) without an associated onset time may have occurred after the initiation of study drug. Hence, adverse events occurring at Randomization (Day 1) with no associated onset time are assumed to be treatment-emergent.

Descriptive summaries of clinical laboratory results will be presented by study visit. Laboratory abnormalities will be graded according to NCI CTCAE. The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized by treatment group and severity grade. Laboratory toxicity shifts from baseline to post-baseline assessments will be summarized by treatment group. Changes from baseline in laboratory tests will be summarized for each treatment group.

Physical examination findings and vital signs will be summarized for any abnormal findings that are considered clinically significant in the opinion of the Investigator. These will be recorded as adverse events or be captured on the medical history if they are already present during Screening. Descriptive summaries of vital signs will be presented by study visit. Descriptive summaries of quantitative changes in vital signs will be presented by treatment group and study visit. Vital sign results will be reviewed for clinically notable abnormalities, according to predefined criteria, and adverse changes will be summarized.

ECG results will be reviewed for clinically notable abnormalities according to predefined criteria. Subjects exhibiting Grade 3 or Grade 4 PR or QTc intervals will be summarized.

Prior and concomitant medications will be mapped to a WHO Drug Dictionary preferred term and study drug classification. The number and percent of subjects taking concomitant medications will be summarized using preferred terms and study drug classifications.

In this study, diarrhea is considered an adverse event and is defined as > 3 unformed stools (BSS score of 6 or 7) per day. If a subject has diarrhea for 2 or more consecutive days and is accompanied by a positive test for *C. difficile* by a testing algorithm (see Figure 10.a.), and received additional standard-of-care CDI therapy, then diarrhea will not be recorded as an adverse event. Instead, it will be considered an on-study recurrent CDI episode and will be included in the determination of efficacy (Section 13.5).

13.7 [redacted]

[redacted]

13.8 Determination of Sample Size

[redacted]

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

In addition to the routine monitoring procedures, the Sponsor or its designees, may conduct audits of clinical research activities in accordance with internal standard operating procedures to evaluate compliance with the principles of ICH GCP. The Sponsor, its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform the Sponsor immediately that this request has been made.

14.1 Monitoring Procedures

Qualified representatives of the Sponsor or its designees (e.g., CRAs) will monitor the study according to a predetermined written monitoring plan. Monitoring visits provide the Sponsor with the opportunities to do the following:

- Evaluate the progress of the study;
- Verify the accuracy and completeness of eCRFs;
- Assure that all protocol requirements, applicable laws and/or regulations, and Investigator's obligations are being fulfilled; and
- Resolve any inconsistencies in the study records.

The Investigator must allow the CRAs to periodically review, at mutually convenient times during the study and after the study has been completed, all eCRFs and office, hospital, study drug, and laboratory records supporting the participation of each subject in the study. The eCRFs and other documentation supporting the study must be kept up-to-date by the Investigator and the research staff at the study site. These study materials must be available for review by the CRA, and/or other qualified representatives of the Sponsor, at each monitoring visit.

Before study initiation, at an initiation visit conducted on site, by video conference, or at an Investigator's meeting, a Sponsor representative will review the protocol, eCRFs, and other study documents with the Investigators and their staff. During the study, the Sponsor CRA or designee will visit the study site regularly to check the completeness of subject records, accuracy of entries on the eCRFs, adherence to the protocol and to ICH GCP, progress of enrollment, and also to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the CRA access to relevant hospital or clinical records to confirm their consistency with the eCRF entries. No information in these records about the identity of the subjects will leave the study center. The Sponsor monitoring standards require full verification for the presence of informed consent, HIPAA authorization, adherence to the Inclusion/Exclusion Criteria, documentation of SAEs, and recording of efficacy and safety variables. Additional checks of the consistency of source data with the eCRFs will be performed according to the study-specific monitoring plan. Representatives of the Sponsor must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, they will review study records and directly compare them with source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable, amongst other duties.

In addition, the study may be evaluated by the Sponsor's internal auditors and government inspectors who must be allowed access to eCRFs, source documents, other study files, and study facilities. Sponsor audit reports will be kept confidential. The Investigator must notify the Sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the Sponsor.

The CRA will follow an "Issue Escalation" process in order to ensure that each issue identified during a monitoring visit is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

14.2 Study Site Training

The Sponsor will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: study background and rationale, clinical data summary, protocol review, ICH GCP, study specific procedures, study drug review, adverse event reporting, eCRFs, study documentation, informed consent process, study monitoring, and enrollment of women of childbearing potential, as applicable.

15.0 ETHICS

15.1 Ethics and Good Clinical Practice

This study will be conducted in compliance with the appropriate protocol, ICH GCP guidelines, the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating study sites must obtain written approval of the study protocol, informed consent documents, other supporting documents, and any advertising for subject recruitment from an appropriate IEC or IRB prior to study initiation. Any amendments to the protocol or consent materials must be approved before they are implemented.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical license, debarment). All potential serious breaches must be reported to the Sponsor immediately. A serious breach is a breach of the conditions and principles of ICH GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

The regulatory files at the study site should contain all required regulatory documents, study-specific documents, and important communications. Regulatory files will be checked at each participating study site for regulatory compliance prior to study initiation, throughout the study, as well as at the study closure.

15.2 Confidentiality Regarding Study Subjects

Applicable data privacy laws and regulations must be adhered to. Investigators must assure that the privacy of subjects, including their personal identity and all personal medical information, will be protected at all times, as required by law. Study sites may be required by their institutions to obtain authorization from subjects for use of Protected Health Information. Study sites will be responsible for communicating with their IRBs/IECs and obtaining the appropriate approvals or waivers to be in regulatory compliance with HIPAA. In eCRFs and other study documents submitted to the Sponsor or its designee, subjects will be identified by their initials, subject number, date of birth, and gender. Personal medical information may be reviewed and/or copied for research, quality assurance, and/or data analysis. This review may be conducted by the CRA, properly authorized persons on behalf of the Sponsor, an independent auditor, IRBs/IECs or regulatory authorities. Personal medical information will always be treated as confidential.

15.3 Future Use of Stored Specimens

Subject stool samples will be collected, stored, and tested as indicated in the protocol. In addition, subjects will be asked to give consent to store samples for future testing within the study, as may be required by emergence of adverse conditions.

15.4 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed ICF, and other information provided to subjects must be reviewed by an IRB/IEC. A signed and dated statement that the protocol, ICF, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects have been approved by the IRB/IEC must be given to the Sponsor before study initiation. The name and occupation of the chairperson and the members of the IRB/IEC (preferred) or the IRB's Health and Human Safety Assurance number must be supplied to the Sponsor or its designee. This committee, as required by local law or procedure, will approve any amendments to the protocol that need formal approval. The IRB/IEC will also be notified of all other administrative amendments (i.e., administrative changes). The Investigator or Sponsor should also provide the IRB/IEC with a copy of the Investigator's Brochure or product labeling, information to be provided to subjects and any updates. The Investigator or Sponsor should provide the IRB/IEC with reports, updates, and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

Study sites will be responsible for maintaining signed ICFs as source documents for quality assurance review and regulatory compliance.

15.5 Informed Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. The Investigator or designee will explain to each subject (or legally authorized representative) the nature of the research study, its purpose, the procedures involved, the expected duration of subject participation, alternative treatment, potential risks and benefits involved, and any discomfort that may occur during the subject's participation in the study. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The ICF should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it and should be given a copy of the signed ICF. No subject can enter the study and no study-related procedures can be done before his/her informed consent has been obtained. The Investigator must submit the ICF with the protocol for IRB/IEC approval.

The Sponsor will supply a proposed ICF template that complies with regulatory requirements, includes all elements required by ICH GCP and applicable regulatory requirements, and is considered appropriate for the study. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki. Any changes to the proposed ICF suggested by the Investigator must be agreed to by the Sponsor or its designee before submission to the IRB/IEC, and a copy of the approved version must be provided to the Sponsor after IRB/IEC approval.

Investigators must:

1. Provide a copy of the ICF and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2. Allow time necessary for the subject or the subject's legally acceptable representative to enquire about the details of the study.
3. Obtain an ICF signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4. Obtain the IRB/IEC's written approval/favorable opinion of the written ICF and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5. If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
6. Revise the ICF whenever important new information becomes available that is relevant to the subject's consent. The Investigator, or a person designated by the Investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.
7. The ICF must also include a statement that the Sponsor and regulatory authorities have direct access to subject records. Subjects unable to give their written consent (e.g., stroke subjects or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subject's understanding, and should he/she become capable, personally sign and date the ICF as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the Investigator. The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

A copy of the signed ICF will be given to the subject for his/her records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

15.6 [redacted]

[redacted]

16.0 DATA HANDLING AND RECORD KEEPING

16.1 Recording of Data and Retention of Documents

All information required by the protocol should be provided; any omissions or corrections should be explained. All eCRFs should be completed within a timely manner, preferably no more than 3 days after the subject's visit, so that the data manager and CRA may check the entries for completeness, accuracy, and legibility. An EDC system will be deployed for this study. The eCRFs will be completed by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites. An electronic version of the final eCRF book for each subject will be forwarded to the study sites for record keeping at the study site closure.

The Investigator must maintain source documents for each subject in the study. All information on eCRFs will be traceable to these source documents, which are generally maintained in the subject's file. The source documents will contain all demographic and medical information, including laboratory data, ECGs, etc., and also a copy of the signed ICF/HIPAA authorization, which should indicate the study number and title of the study. Essential documents, as listed below, will be retained by the Investigator for the maximum period required to comply with national and international regulations, or institutional procedures, or for the period specified by the Sponsor, whichever is longer. The Sponsor will notify the Investigator(s)/institution(s) when study-related records are no longer required to be retained. The Investigator agrees to adhere to the document retention procedures by signing the protocol. The Investigator must contact the Sponsor prior to destroying any records associated with the study.

If the Investigator withdraws from the study (e.g., relocation or retirement), the records shall be transferred to a mutually agreed-upon designee (e.g., another Investigator or IRB). Notice of such transfer will be given in writing to the Sponsor. Essential documents include:

1. Signed protocol and all amendments,
2. IRB/IEC approvals for the study protocol and all amendments,
3. All source documents and laboratory records,
4. eCRF copies,
5. Subjects' ICF/HIPAA authorizations, and
6. Any other pertinent study documents.

16.2 Case Report Forms

[redacted]

16.3 Data Management

16.3.1 [redacted]

[redacted]

16.3.2 Data Errors

Errors, omissions, or requests for clarification at the study site will be queried; queries will be entered into the EDC system for resolution by study sites.

16.3.3 [redacted]

[redacted]

16.4 [redacted]

[redacted]

17.0 [redacted]

[redacted]

18.0 [redacted]

[redacted]

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20.0 APPENDICES

20.1 Electronic Product Labels for Standard CDI Antibiotics

20.1.1 Oral Vancomycin

http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/50606slr020_vancocin_lbl.pdf

20.1.2 Fidaxomicin

https://www.merck.com/product/usa/pi_circulars/d/dificid/dificid_pi.pdf

20.1.3 Metronidazole

http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/12623slr059_flagyl_lbl.pdf